

Serial No. 10/549,707
Declaration dated
Reply to Final Office Action of August 10, 2007

Docket No. 4439-4036

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Masataka KUWANA, et al.

Group Art Unit: 1649

Serial No.: 10/549,707

Examiner: Dutt, Aditi

Filed: October 27, 2005

Confirmation: 2198

For: MONOCYTE-ORIGIN MULTIPOTENT CELL MOMC

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is a Declaration under 37 C.F.R. §1.132 by Masataka Kuwana, MD, Ph.D. in the above-identified application.

I, the undersigned, Masataka Kuwana, declare and state that:

1. I am a co-inventor of the subject patent application having serial no. 10/549,707.
2. My education and professional experience as an expert in the area of tissue engineering are set forth on the attached copy of my Curriculum Vitae.

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3. I have read and understand U.S. Patent Application Serial No. 10/549,707, entitled "MONOCYTE-ORIGIN MULTIPOTENT CELL MOMC," and I submit this Declaration in its support.

4. I have read and understand the August 10, 2007 Final Official Action issued in the above-identified case.

5. I have read and understand the publication of Zhao, et al. (*PNAS*, 100: 2426-2431, 2003) cited by the Examiner.

6. In particular, I understand that in the August 10, 2007 Final Official Action, the Examiner has rejected claims 2-8 because they are anticipated by Zhao, et al. Specifically, the Examiner states that the Zhao, et al. reference teaches the isolation of pluripotent stem cells (PSC) from human peripheral blood monocytes that resemble fibroblasts and express the monocytic and hematopoietic cellular differentiation stem cell markers, such as CD14, CD34 and CD45. The Zhao, et al. reference allegedly further discloses that human peripheral blood cells containing monocytes, when cultured under specific conditions, differentiate into macrophages, lymphocytes, epithelial, neuronal, endothelial and hepatocytes (Final Office Action- pages 3-6). As a person skilled in the art, I respectfully disagree with the Examiner's rejection.

7. The inventors of the instant application attempted the differentiation induction of MOMC into T-cells using IL-2, as described in Zhao, et al. The expression of CD3 was analyzed with a flow cytometry technique. The results, as shown in Figure 1 below, demonstrate that CD3 was not expressed. Thus, MOMC does not differentiate into T-cell using the method described in Zhao, et al.. Furthermore, the inventors attempted the differentiation induction of

MOMC into neuronal cells, epithelial cells and hepatocytes using NGF, EGF and HGF, respectively. When MOMC was immunostained with an immunoenzymatic method, no brown coloration of MOMC was observed. As shown in Figure 1 below, MAP2 (a marker of neuronal cells), keratin (a marker of epithelial cells), and albumin (a marker of hepatocytes), were not expressed. Hence, it was shown that MOMC does not differentiate into neuronal cells, epithelial cells or hepatocytes. These results show that MOMC are clearly distinct from PSC.

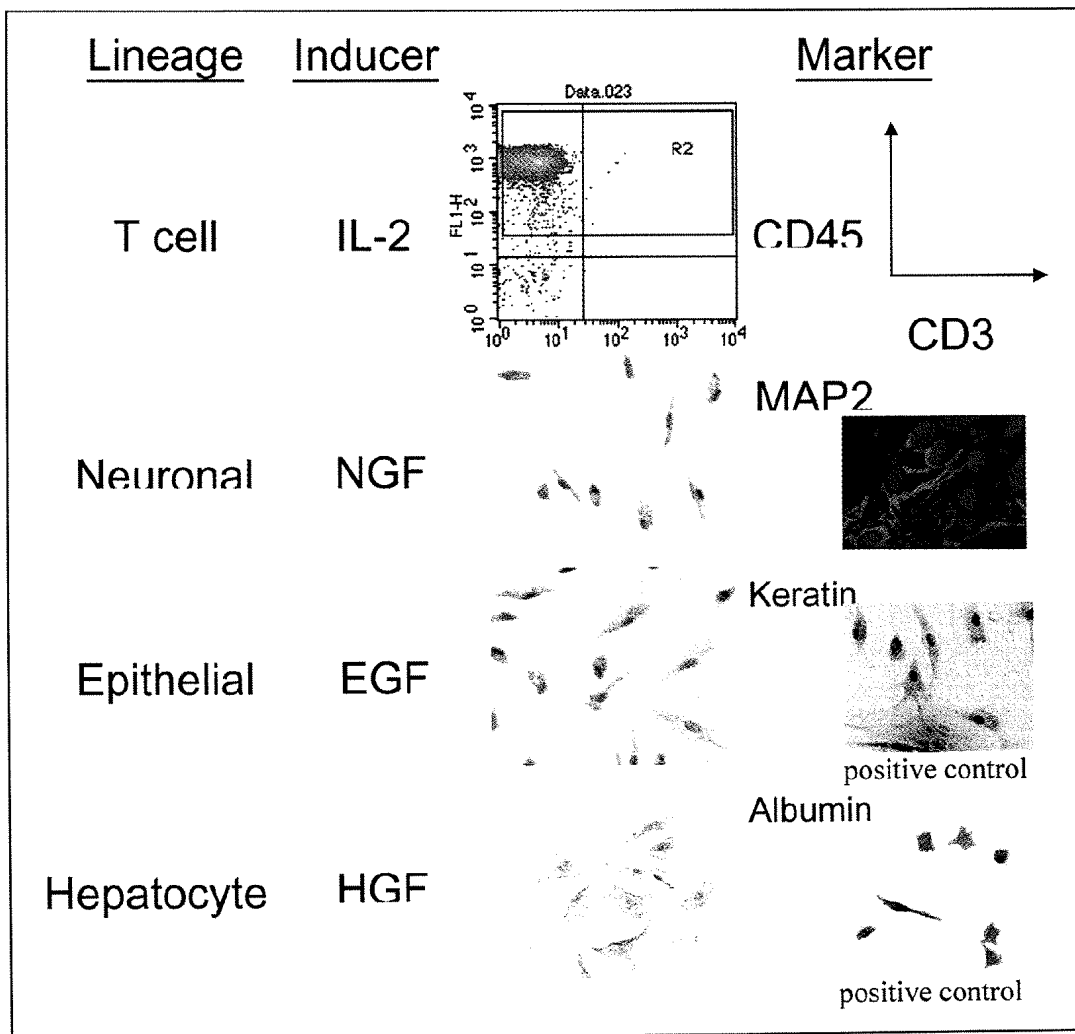


Figure 1: Results of experiments concerning differentiation abilities of human MOMC cultured under the differentiation conditions of PSC into T-cells, neuronal cells, epithelial cells and hepatocytes.

8. Finally, the inventors have also carried out a check experiment, and the results of Zhao, et al. were not reproducible¹. The steps of the check experiments carried out by the inventors are set forth here. Monocytes were cultured according to the method of Zhao, et

¹ Reproducibility is solely based on the disclosure of Zhao, et al. and does not mean that there is no reproducibility in Zhao, et al. when special techniques or materials are used but not disclosed in their article.

al.(with medium containing M-CSF and LIF), and cells morphologically resembling fibroblasts were observed. However, the frequency of the “cells that morphologically resembled fibroblasts” was much lower than that described in Zhao, et al., and though their cloning was attempted through the method described in Zhao, et al, the cells did not proliferate and clone. The data, therefore, which should be obtained from their separation, purification and analysis were not available. Moreover, their flow cytometry analysis showed a slight expression of CD34 in the cells, which is within the margin of error of flow cytometry analysis. The expression of CD34 was not detected with either immunostaining or the RT-PCR method as shown in Zhao, et al. Furthermore, the inventors confirmed that the cells cultured according to the method of Zhao, et al., which include the “cells that morphologically resembled fibroblasts,” did not express CD3 in the presence of IL-2, vWF in the presence of EGF, or AFP in the presence of HGF. These cells also did not differentiate into osteoblasts, skeletal myoblasts or chondrocytes under the differentiation induction conditions of MOMC set forth in the instant application.

9. Zhao et al. disclose pluripotent stem cells (PSC) which express CD14, CD34 and CD45. Zhao et al. also describe that PSC differentiate into macrophages, lymphocytes, epithelial cells, neuronal cells, endothelial cells and hepatocytes. However, the Monocyte-Origin Multipotent Cells (MOMC) of the instant invention are much different from PSC of Zhao et al. in their properties, especially their differentiation abilities as demonstrated in Table 1 below.

TABLE 1.

	PSC	MOMC
Differentiation Abilities		
T-lymphocyte	+	-
epithelial cell	+	-
endothelial cell	+	+
neuronal cell	+	Culture under NGF stimulation (culture condition of PSC): - Coculture with rat neurons: +
hepatocyte	+	-
mesenchymal cell	not reported	+
proliferation from a single cell (cloning)	possible	impossible

The "+" and "-" signs show whether human MOMC cultured under the differentiation condition of PSC has a differentiation ability or not.

10. In view of the evidence presented above, there is a clear difference in differential abilities between MOMC and PSC. Furthermore, the cells of Zhao, et al. do not express vWF in the presence of EGF and do not differentiate into osteoblasts, skeletal myoblasts or chondrocytes under the differentiation induction conditions of MOMC. Therefore, one skilled in the art would conclude that MOMC is clearly distinct from said "cells that morphologically resembled fibroblasts" (Zhao, et al. page 2427, column 1, 3rd paragraph).

11. Thus, it is my experience and my opinion, as one skilled in the art of tissue engineering, that MOMC and PSC cells are not identical, in view of the differences in the differential abilities of these cells. These differences of differential abilities necessarily result in the differences of diseases for which these cells will be used as a transplant in the future. It is

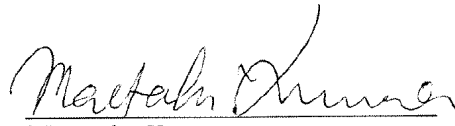
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clear from these points that the instant invention could not be anticipated by the teachings of Zhao, et al.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issuing thereon.

Respectfully submitted,

Date : _____


Masataka Kuwana

July 1, 2007

CURRICULUM VITAE

NAME:

Masataka Kuwana

ACADEMIC TITLE:

Associate Professor

SEX:

Male

BIRTH DATE:

May 16, 1963

BIRTHPLACE:

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EDUCATION:

<u>Institution and Location</u>	<u>Degree</u>	<u>Year Conferred</u>	<u>Field of Study</u>
Keio University School of Medicine Tokyo, Japan	MD	May, 1988	Medicine
Keio University School of Medicine Tokyo, Japan	PhD	January, 1992	Cell biology Immunology

BOARD CERTIFIED MEMBERS:

1994	Board Certified Member of the Japanese Society of Internal Medicine
1995	Board Certified Member of the Japanese College of Rheumatology
1995	Fellow of the Japanese Society of Internal Medicine
2005	Instructor of the Japanese College of Rheumatology

RESEARCH AND PROFESSIONAL EXPERIENCE:

1988-1992	Graduate student, Keio University School of Medicine, Tokyo, Japan
1992-1993	Postdoctoral Fellow, Division of Rheumatology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan
1993-1996	Postdoctoral Research Fellow, Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA

1996-1998	Instructor, Division of Rheumatology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan
1998-2000	Instructor, Institute for Advanced Medical Research, Keio University School of Medicine, Tokyo, Japan
2000-2005	Assistant Professor, Institute for Advanced Medical Research, Keio University School of Medicine, Tokyo, Japan
2006-Present	Associate Professor and Chief, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan

AWARD:

	<u>Source</u>	<u>Type of Support</u>
1993-1994	Arthritis Foundation, Western Pennsylvania Chapter	Research Fellowship Award
1995	American Clinical Research Meeting	Travel Award
1995	American College of Rheumatology	Senior Rheumatology Scholar Award
1998	Naito Foundation	Research Award
1999	Japanese Intractable Diseases Foundation	Research Prize
2000	Sakaguchi Research Foundation	Research Award
2001	Ichiro Kanehara Foundation	Research Prize
2001	Mochida Memorial Foundation	Research Award
2001	Uehara Life Science Foundation	Research Award
2002	Keio University School of Medicine Sanshikai	Yong Investigator Award
2002	Terumo Life Science Foundation	Research Award
2002	Nagao Memorial Fund	Research Prize
2003	Japan Rheumatism Association	Research Award
2004	Japanese Society for Connective Tissue Research	Otake Memorial Prize
2005	Keio University Intellectual Program Center	Honorary Award
2005	Takeda Science Foundation	Research Award
2005	Keio University School of Medicine Sanshikai	Kitajima Memorial Prize
2007	International Systemic Sclerosis	Travel Award

2007 Forum 2007
Japan Rheumatism Foundation Research Prize

EDITORIAL BOARD:

2001-2005 Editorial Board, Connective Tissue
2002-2005 Editorial Board, Japanese Journal of Clinical Immunology
2004-now International Editor, Drugs
2005-now Advisory Editor, Arthritis and Rheumatism
2006-now Editorial Board, Journal of Infectious Diseases

MEMBER:

American College of Rheumatology
American Association of Immunologists
New York Academy of Science
Japanese Society of Internal Medicine
Japanese College of Rheumatology
Japanese Society for Immunology
Japan Society for Clinical Immunology
Japanese Society of Clinical Hematology
Japanese Society for Connective Tissue Research
Japanese Society for *Helicobacter* Research
Japanese Society of Inflammation and Regeneration

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- Authors' reply (letter). *Ann. Rheum. Dis.* 2001; 60(9): 897-898.
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